IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Fleischer and Reimer	Confirmation No.: 8087
Serial No.: 09/701,220	Art Unit: 1615
Filed: November 27, 2000	Examiner: Gollamudi S. Kishore
For: PREPARATIONS FOR THE PROMOTION OF WOUND HEALING IN THE UPPER RESPIRATORY TRACT AND/OR EAR (AS AMENDED)	Attorney Docket No.: 11390-004

DECLARATION OF DR. WOLFGANG FLEISCHER UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Wolfgang Fleischer, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application.

2. I am currently General Manager of Mundipharma Research, GmbH & Co. KG, Limburg, Germany, which is an associated company of EURO-CELTIQUE S.A., the assignee of the above-identified patent application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit 1.

4. I have reviewed the above-identified patent application, the pending claims, and the Office Action mailed November 26, 2002. I understand that the Examiner has rejected the claims, *inter alia*, under 35 U.S.C. § 103(a) on the allegation that the claimed subject matter is obvious over the disclosure of European Patent No. EP 639373 (the '373 patent"), alone, or in combination with U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight").

5. The aim of wound treatment is generally to keep the number of microorganisms in the wound as low as possible in order to prevent infection and sepsis, and at the same time, to stimulate the repair process in order to achieve optimum healing and quality of wound closure, including restoring the tissue at the wound site to its original appearance and function. However, agents that stimulate healing, which are largely based on maintaining moisture content, are usually contraindicated in the presence of a potential infection since moist treatment of wounds increases risk of bacterial infection. Additionally, antiseptics and antibiotics are mostly inhibitory to granulation or epithelialization. Thus, there has been a need in the art for treatments to both stimulate wound healing and prevent infection without inhibiting the other.

6. I have reviewed the '373 patent, of which I am a co-inventor. The '373 patent teaches that liposomes containing povidone iodine can be administered externally, *i.e.*, to the skin or eye, for treatment of an infection. Further, the '373 patent teaches that when liposomes containing povidone iodine also contain a wound healing promoting agent, such liposomes can also be used to treat an infection and to promote wound healing. A person of ordinary skill in the art, upon reading the '373 patent, would recognize that in order to externally treat an infection and promote the healing of an external wound, liposomes containing both povidone iodine and a wound healing promoting agent need to be administered to the site of the wound. The '373 patent discloses on page 3, line 15 that such wound healing promoting agents include compounds such a vitamins, allantoin and some azulenes. Thus, the '373 patent teaches that promoting wound healing is not the result of the application of liposomes containing povidone iodine, but, rather, is the result of the application of liposomes also containing a wound healing promoting agent. There is no disclosure in the '373 patent that teaches or suggests that liposomes containing povidone iodine alone can be used without a wound healing promoting agent for promoting the healing of wounds or for suppressing undesired tissue formation (suppressing scar formation) or for restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract or ear.

7. It was well known prior to the filing of the present application that iodine and iodine-containing compounds such as povidone iodine are highly oxidizing agents that have been used as topical disinfectants and anti-infectants. Further, although povidone iodine and liposomes containing povidone iodine have been applied externally, their internal application

to more sensitive tissue, especially lung tissue, was taught away by the art in view of the known harsh oxidative nature of iodine and the known ability of iodine and iodine compounds to damage and/or kill cells. It was also known in the art that iodine and iodine compounds can adversely effect wound healing. Lineaweaver *et al.*, 1985, Arch Surg 120:257-270 (which is attached hereto as Exhibit 2) disclose that povidone iodine significantly retarded wound healing. Kallenberger *et al.*, 1991, Hyg + Med 16:383-395 (which is attached hereto as Exhibit 3) disclose that application of antiseptics, such as the iodophores Braunol® and Betadine®, significantly reduced proliferation rates of epithelial cells. Thus, in view of the teachings of the prior art, a skilled artisan would not have been motivated to apply iodine compounds to external wounds in order to enhance wound healing.

8. Much of the tissue in the upper and lower respiratory tract is lined with ciliated cells, which cells are required for proper lung function. The cilia on the cell move (beat) in unison (frequency of about 16 Hz) to expel mucous and contaminants from the respiratory tract. In situations where cilia function is impaired, respiratory tract function is impaired, which can lead to disease and eventually death. Cystic fibrosis is one exemplary disease caused by malfunctioning cilia. In view of the importance of not harming ciliated cells and in view of the known ability of iodine compounds to damage cells, one skilled in the art would not have been motivated to apply iodine compounds to the respiratory tract for any reason for fear of damaging the ciliated cells.

9. However, contrary to the expectations of the art, it has been shown by my co-inventor and me that the application of liposomes containing povidone iodine to ciliated lung cells *in vitro* does not result in damage to the cells or inhibition of cilia function. As detailed on pages 23-24 of the specification, the results of Test IV demonstrate that when ciliated epithelium cells were exposed to 5% or 2.5% povidone iodine in solution, no ciliary activity was subsequently observed, *i.e.*, the cells were damaged or killed. However, when the cells were exposed to liposomes with 4.5% povidone iodine, no difference in ciliary activity was seen as compared to the control cells. It is my opinion as a skilled artisan that since liposomes containing povidone iodine did not damage ciliated cells in culture, liposomes containing povidone iodine will not damage internal respiratory tract tissue, in which such ciliated cells can be found.

10. Further, contrary to the expectation in the art, liposomes containing povidone iodine without a wound healing promoting agent have been unexpectedly shown to suppress

undesired tissue formation, such as scars, and to restore the original appearance of tissue at a site of tissue damage, which following post-filing date references clearly demonstrate: Vogt *et al.*, 2001, Wound Rep. Reg. 9:116-122 ("Vogt"), Reimer *et al.*, 2000, Dermatology 201:235-241 ("Riemer"); and Integrated Final Study Report for HOM3401, Efficiency and Tolerability of PVP-iodine-liposome-hydrogel (Hydrosom) in the treatment of acute transplantation wounds by Prof. Dr. P. Vogt, May 8, 2003 ("Final Study"). I am informed that copies of these references are being made of record in a Supplemental Information Disclosure Statement being submitted concurrently with this Declaration.

11. Vogt discusses a comparative study between the effects of a hydrogel formulation of liposomes containing povidone iodine and chlorohexidine gauze administration to patients receiving meshed skin grafts after burns or reconstructive procedures. The results of the study showed that wounds treated with the povidone iodine containing liposome formulation showed less graft loss, earlier epithelialization and better healing of the wounds than those wounds treated with the conventional gauze. See, the Abstract. Further, Vogt discloses on page 119, left column, that control treatment of the graft site resulted in significant formation of scabs in the mesh holes, whereas those grafts treated with liposomes containing povidone iodine resulted in a clean and smooth surface almost without scab formation. Applicants submit that these results indicate that application of liposomes containing povidone iodine are able to suppress undesired tissue formation as well as restore the original appearance of tissue at a site of tissue damage.

12. Reimer discloses the results of a proof of concept phase II study wherein primary wounds of different origin were treated with a hydrogel formulation of liposomes containing povidone iodine and compared to treatment with povidone iodine alone. As discussed on page 240, left column, the results indicated that the graft take rate appeared to be improved and the wounds closed more rapidly when treated with liposomes containing povidone iodine.

13. The Final Study summarizes the results of a clinical trial of wound treatment with a povidone iodine liposome hydrogel and fat gauze as compared to treatment with a fat gauze. The results of the trial clearly showed that treatment with the povidone iodine liposome hydrogel results in better wound healing and significant less transplant losses. Final Study, page 95.

14. It is my opinion as a skilled artisan that the foregoing experimental evidence showing the promotion of wound healing and suppression of undesired tissue growth by liposomes containing povidone iodine would be predictive to one of skill in the art that liposomes containing povidone iodine can suppress undesired tissue formation or restore the original appearance of tissue at the site of tissue damage in the upper respiratory tract or ear. It is also my opinion as a skilled artisan that one skilled in the art would have no reason to doubt that a composition which suppresses undesired tissue formation in the epidermis and underlying epithelial cell layer would not also suppress undesired tissue formation in the upper respiratory tract and/or ear.

15. As explained in ¶ 6 above, the '373 patent teaches that liposomes containing povidone iodine can be administered externally, *i.e.*, to the skin or eye for the treatment of an infection. Further, when the liposomes also contain wound healing promoting agents, the liposomes can be used to promote wound healing. There is no disclosure in the '373 patent that teaches or suggests that liposomes containing povidone iodine alone can be used for promoting the healing of wounds or suppressing undesired tissue formation, *e.g.*, suppressing scar formation. Moreover, as explained in ¶ 7 above, the prior art taught away from using iodine compounds in wound healing as publications reported that iodine compounds inhibited wound healing. Further, there is no teaching or suggestion that liposomes containing povidone iodine can be administered to internal body parts. The mucosa of the eye is not considered an internal body part. In fact, as discussed in ¶ 8, the prior art taught away from applying any iodine compound to respiratory tract tissue, for any reason, for fear of damage to the tissue by the iodine compound.

16. I have reviewed the Knight reference. This publication discloses that liposomes can be administered to the respiratory tract. It is my belief that none of the compounds that are taught to be formulated with liposomes in this reference is in the same class of compounds as povidone iodine, which is a highly oxidative chemical antiseptic agent. It was well know to the skilled artisan prior to the filing date of present invention that povidone iodine is a highly oxidizing agent that has been used as a topical anti-infective and disinfective. Knight does not teach or suggest that any such oxidizing compounds can be formulated with liposomes and applied to the lungs. Contrary to the Examiner's unsupported allegation, as a skilled artisan it is my belief that administration of the liposomal formulations of Knight are not suggestive of administration of liposomal formulations of povidone iodine to the upper respiratory tract and/or non-external parts of the ear because the compounds

formulated with liposomes by Knight are not in the same class of compounds to which povidone iodine belongs. Further, Knight does not teach or suggest the claimed methods for promoting wound healing and suppressing undesired tissue formation or restoring the original appearance of tissue at a site of tissue damage in the upper respiratory tract and/or ear.

17. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: 28.2.2005

Wolfgang Fleischer

Wolfgang Fleischer